this tumour-type was diagnosed in only a small fraction of patients, 3 of 4 responders were patients with endometrioid adenocarcinomas. This strongly suggests that endometrioid adenocarcinoma may behave in a similar way as endometrial adenocarcinoma as hormone-sensitive tumours. In view of this finding, the possible risk of hormone-replacement therapy containing oestrogens should be discussed.

References

1. Kristensen GB, Tropé C. Epthelial ovarian carcinoma. *Lancet* 1997, **349**, 113–117.
2. Laco JS, Schwartz PE, MacLusky NJ, Labaree DC, Eisenfeld AJ. Antiproliferative actions of tamoxifen to human ovarian carcinomas *in vitro*. *Cancer Res* 1984, **44**, 2266–2271.
3. McClay EF, Albright KD, Jones JA, Christen RD, Howell SB. Tamoxifen delays the development of resistance to cisplatin in human melanoma and ovarian cancer cell lines. *Br J Cancer* 1994, **70**, 449–452.
4. Williams HC. Tamoxifen in relapsed ovarian cancer: a systemic review. *Int J Gynecol Cancer* 1998, **8**, 89–94.
5. Abu-Jawdeh G, Jacobs T, Niloff J, Cannistra S. Oestrogen receptor expression is a common feature of ovarian borderline tumors. *Gynecol Oncol* 1996, **60**, 301–307.
6. Anderl P, Fuith L, Daxenbichler G, *et al*. Correlation between steroid hormone receptors, histological and clinical parameters in ovarian carcinoma. *Gynec Oncol Investig* 1988, **25**, 135–140.
7. Beecham J, Blessing J, Creasman W, Hatch K. Tamoxifen responsiveness, hormone receptors, and tumor grade: a prospective study. *Gynecol Oncol* 1988, **29**, 136, (Abstract 24).
8. Marth C, Sorheim N, Kaern J, Tropé C. Tamoxifen in treatment of recurrent ovarian carcinoma. *Int J Gyncol Cancer* 1997, **7**, 256–261.
9. Schwartz PE, Keating G, MacLusky N, Naftolin F, Eisenfeld A. Tamoxifen therapy for advanced epithelial ovarian cancer. *Obstet Gynecol* 1982, **59**, 583–587.
10. Landoni F, Epis A, Gorga G, Regallo M, Vassena L, Mangioni C. Hormonal treatment in advanced epithelial ovarian cancer. In Pamutti F, ed. *Anti-oestrogen in Oncology. Past, Present and Prospects*. Amsterdam, New York, Oxford, Excerpta Medica, 1985, 262–265.
11. Shirey DR, Kavanagh JJ, Gershenson DM, Freedman RS, Copeland LJ, Jones LA. Tamoxifen, therapy of epithelial ovarian cancer. *Obstet Gynecol* 1985, **66**, 575–851.
12. Slevin ML, Harvey VJ, Osborne RJ, Sheperd JH, Williams CJ, Mead GM. A phase II study of tamoxifen in ovarian cancer. *Eur J Cancer Clin Oncol* 1987, **22**, 309–312.
13. Weiner SA, Alberts DS, Surwitt EA, Davis J, Grosso D. Tamoxifen therapy in recurrent epithelial ovarian carcinoma. *Gynecol Oncol* 1987, **27**, 208–213.
14. Belinson JL, McClure M, Badger G. Randomized trial of megestrol acetate vs megestrol acetate/tamoxifen for the management of progressive or recurrent epithelial ovarian carcinoma. *Gynecol Oncol* 1987, **28**, 151–155.
15. Markman M, Iseminger KA, Hatch KD, Creasman WT, Barnes W, Dubeshter B. Tamoxifen in platinum-refractory ovarian cancer. A Gynecologic Oncology Group ancillary report. *Gyncol Oncol* 1996, **62**, 4–6.
16. Hatch KD, Beecham JB, Blessing JA, Creasman WT. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. *Cancer* 1991, **68**, 269–272.
17. Osborne RJ, Malik ST, Slevin ML, *et al*. Tamoxifen in refractory ovarian cancer. The use of a loading dose schedule. *Br J Cancer* 1988, **57**, 115–116.
18. Pagel J, Rose C, Thorpe S, Hald I. Treatment of advanced ovarian carcinoma with tamoxifen. A phase II trial. *Proc 2nd Eur Conf Clin Oncol* 1983, **42**, (Abstracts).
19. Hammerlynck JVTH, Vermorken JB, Van der Burg MEL. Phase II study of tamoxifen in advanced ovarian cancer. *Proc 3nd Eur Conf Clin Oncol* 1985, **43**, (Abstract).
20. Cambell JJ, Rome RM, Quinn MA, Pepperrell RJ, Morgan WJ. Tamoxifen for recurrent progressive epithelial ovarian tumours. *Proc XI Clin Oncol Soc Australia* 1984, **73**, (Abstract).
21. Rowland K, Bonomi P, Wilbanks G, Yordan E, Graham J, Dunne C. Hormone receptors in ovarian carcioma. *Proc Am Soc Clin Oncol* 1985, **456**, (Abstract).
22. Jakobsen A, Bertelsen K, Sell A. Cyclic hormonal treatment in ovarian cancer. A phase II trial. *Eur J Cancer Clin Oncol* 1987, **23**, 915–916.
23. Ahlgren JD, Ellison NM, Gottlieb RJ, *et al*. Hormonal palliation of chemoresistant ovarian cancer: three consecutive phase II trials of the Mid-Atlantic Oncology Program. *J Clin Oncol* 1993, **11**, 1957–1968.
24. Jager W, Sauerbrei W, Beck E, *et al*. A randomized comparison of triptorelin and tamoxifen as treatment of progressive ovarian cancer. *Anticancer Res* 1995, **15**, 2639–2642.
25. Van Der Velden J, Gitsch G, Wain G, *et al*. Tamoxifen in patients with advanced epithelial ovarian cancer. *Int J Gyncol Cancer* 1995, **5**, 301–305.
26. Gennatas C, Dardoufas C, Karvouni H, *et al*. Phase II trial of tamoxifen in patients with advanced epithelial ovarian cancer. *Am Soc Clin Oncol* 1996, **15**, 287, (Abstract 782).

Toremifene: where do we stand?

J. Mäenpää [a,*], K. Holli [b], T. Pasanen [c]

[a] *Departments of Obstetrics and Gynecology, and Oncology and Radiotherapy, University Hospital, PO Box 2000, FIN-33521 Tampere, Finland*
[b] *Departments of Obstetrics and Gynecology, University Hospital, PO Box 2000, FIN-33521 Tampere, Finland*
[c] *Orion Pharma, Espoo, Finland*

* Corresponding author. Tel.: +358-3-247-5111; fax: +358-3-247-4360.
E-mail address: juhani.maenpaa@tays.fi (J. Mäenpää).

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Abstract

Toremifene is a chlorinated triphenylethylene that is indicated for postmenopausal breast cancer. For advanced disease, toremifene has been found to be as effective and at least as well tolerated as tamoxifen. The same appears to apply for adjuvant setting. After a total cumulative clinical exposure to toremifene of approximately 140 000 patient-years, only 9 cases of endometrial carcinoma have been reported. The annual hazard rate (per 1000 patient-years) of developing endometrial carcinoma in breast cancer patients on adjuvant toremifene is 1.14 (versus tamoxifen 2.0 and placebo 0.4). Although toremifene (being a partial agonist) may unmask pre-existing endometrial tumours, there is no clinical data implying that it would *per se* cause endometrial carcinoma.

Keywords: Tamoxifen; Toremifene; Postmenopausal breast cancer; Endometrial carcinoma

1. Introduction

Toremifene is a chlorinated triphenylethylene that is indicated for postmenopausal breast cancer. The first clinical trials were initiated in 1982, and toremifene has been approved for clinical use since 1988 in Finland, since 1994 in Japan (30% market share), and since 1997, in the EU, the US and Mexico.

In phase II trials, the objective response rate of oestrogen receptor (ER)-positive or ER-unknown postmenopausal breast cancer to toremifene 60 mg/day was 48–50% [1]. A recent meta-analysis of phase III trials (1421 patients) showed that toremifene 40–60 mg/day is as effective as tamoxifen 20–40 mg/day (response rates 24.0 and 25.3%, respectively, $P = 0.675$) [2]. The treatments were well tolerated, but more patients on tamoxifen (20%) than on toremifene (14%, $P = 0.007$) discontinued the treatment prematurely.

Toremifene has been studied also in adjuvant setting. An interim analysis of the first 900 patients with a mean follow-up of 3 years in the Finnish adjuvant trial (toremifene 40 mg/day versus tamoxifen 20 mg/day for 3 years) has been published [3]. Total recurrence rates were 18.3% in toremifene and 21.3% in tamoxifen group ($P = 0.26$). No significant differences in acute toxicity were found.

As of 31 August, 1999 only 9 cases of endometrial carcinoma in patients treated with toremifene (8 for breast cancer and 1 for desmoid tumour) have been reported. 5 of them had received toremifene for less than 1 year, and the rest for 1 year or longer. 2 patients had previously been on long-term tamoxifen. The annual hazard rate (per 1000 patient-years) of endometrial carcinoma in postmenopausal breast cancer patients treated with toremifene is given in Table 1.

It is in essence, the same as it was 1 year previously with a 30 000 patient-years smaller exposure to toremifene [4]. The hazard rate in patients on adjuvant toremifene (1.14) lies in between the hazard rates for adjuvant tamoxifen and placebo (2.0 and 0.4, respectively) [4].

Table 1
Annual hazard rate (per 1000 patient-years) of developing endometrial carcinoma in postmenopausal breast cancer patients treated with toremifene

	Adjuvant trials	All trials[a]	Cumulative total exposure
Dose (mg/day)	40–60	200–300	
n of patients	1257	3552	
n of patient-years	3513	7015	140 329
n of events	4	7	8
Annual hazard rate	1.14	1.0	0.06
95% CI	(0.44279, 2.92796)	(0.48337, 2.05996)	

[a] Trials for advanced cancer and adjuvant therapy, combined.

2. Conclusion

Toremifene is at least as effective and acutely as well tolerated as tamoxifen in postmenopausal breast cancer. Although toremifene (being a partial agonist) may unmask pre-existing endometrial tumours, there is no clinical data implying that it would *per se* cause endometrial carcinoma.

References

1. Mäenpää JU, Ala-Fossi S-L. Toremifene in postmenopausal breast cancer. Efficacy, safety and cost. *Drugs & Aging* 1997, **11**, 261–270.
2. Pyrhönen S, Ellmén J, Vuorinen J, *et al*. Meta-analysis of trials comparing toremifene with tamoxifen and factors predicting outcome of antiestrogen therapy in postmenopausal women with breast cancer. *Breast Cancer Res Treat* 1999, **56**, 133–143.
3. Holli K, Joensuu H, Valavaara R, *et al*. Interim analysis of the Finnish toremifene vs tamoxifen adjuvant trial. *Breast Cancer Res Treat* 1998, **50**, 283.
4. Mäenpää J, Ellmén J, Pasanen T, Kaukonen M. Re: effects of the antiestrogens tamoxifen, toremifene, and ICI 182,780 on endometrial cancer growth. *J Natl Cancer Inst* 1999, **91**, 972–973.